

maternal infant  
child & youth  
research network



réseau de recherche  
en santé des  
enfants et des mères

# Canadian Pediatric Clinical Trials Activity 2005-2009

Report completed August 2010

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## Introduction

On average, a Canadian child receives 4 prescriptions a year from a range of more than 1200 different drugs. 75% of these drugs do not have dosing or safety data for use in children.

Internationally, there is a focus on children's medicines with the intent to optimize the development, wider availability, and routine use of effective, safe, and affordable medicines addressing important child health needs. Milestone developments unfolding in recent years include the formation of an International Alliance for Better Medicines for Children in 2006 and landmark initiatives by the European Union (EU), the World Health Assembly (WHA), and the WHO in 2007. An EU Paediatric Regulation entered into force January 26<sup>th</sup>, 2007<sup>1</sup> with the objective *“to improve the health of children in Europe by facilitating the development and availability of medicines for children from birth to less than 18 years, ensuring that medicines for use in children are of high quality, ethically researched, and authorised appropriately, improving the availability of information on the use of medicines for children, without subjecting children to unnecessary trials, or delaying the authorisation of medicinal products for use in adults.”* In May 2007, the 60<sup>th</sup> World Health Assembly resolved that drug development for children was a priority and passed a resolution on Better Medicines for Children (WHA60.20) that described several strategies to improve access to essential medicines of adequate quality for children. In February 2009, the European Medicines Agency launched a European network of existing national and European paediatric research networks and centres to support research in children, particularly in relation to paediatric (drug) investigation plans.<sup>2</sup> In the USA, the Federal Food, Drug, and Cosmetic Act (as amended by the Food and Drug Administration Modernization Act of 1997 (FDAMA) and the 2002 Best Pharmaceuticals for Children Act (BPCA), provides incentives to companies who perform research to determine the safety, efficacy, dosing and unique risks associated with medications for children, based on the same level of scientific evidence required for adults.

Canada (along with many other countries) has not yet adopted a formal position on drug development and clinical trials in children. And yet, there is considerable expertise in this country in pediatric clinical pharmacology, clinical trials, outcomes research and bioethics. Canada has been a world leader in pediatric pharmacology and pharmacy with particular expertise in relevant clinical areas and in the development of appropriate clinical trial methods. This expertise has developed over the past 30 years and is recognized through the involvement of Canadian experts with international agencies such as WHO and UNICEF. Canadian expertise is also supported by the International Federation of Pharmaceutical Manufacturer Associations and by the European Community, European Medicines Evaluation Agency. Furthermore, Canadian experts have been engaged in efforts with the International Conference of Drug Regulatory Associations to improve the regulatory framework supporting the development of improved drug therapy for infants, children, and youth worldwide. Canadian academics are also experts in educational methods and knowledge transfer to support more effective drug

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<sup>1</sup>[http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/document\\_listing/document\\_listing\\_000068.jsp&jsenabled=true](http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/document_listing/document_listing_000068.jsp&jsenabled=true)

<sup>2</sup> <http://www.emea.europa.eu/htms/human/paediatrics/network/html>

investigation and consequently better health outcomes for children worldwide. Moreover, Canada has the second largest concentration of biotechnology companies in the world, employing around 40,000 people. A further 35 000 indirect jobs come from this industry.<sup>3 4</sup> In 2005, the number of Canadian biotechnology companies grew to a total of 532, an increase of 9 percent since 2003 and revenues were CDN\$4.2 billion, a 9 percent increase over 2003 revenues.<sup>5</sup> Industry Canada considers the pharmaceutical industry to be “*one of the most innovative and profitable industries in Canada*”, reporting that the Canadian Pharmaceutical and Biotechnology industry is a 14.7 billion dollar industry with a 14% compounded growth over the last five years.<sup>6</sup> Industry Canada Life Sciences Gateway Sector Profile II section<sup>7</sup> posts the following information:

- ❖ Total business expenditures on research and development by Canadian pharmaceutical companies reached \$1.25 billion in 2005.
- ❖ The pharmaceutical industry is second after the Information Technology (IT) sector in R&D intensity. Thirty-three pharmaceutical and biotechnology companies are listed in Research Infosource’s Top 100 Corporate R&D Spenders 2005 in Canada. The leading spender, Apotex, ranks 11th, with over \$172 million spent on R&D. Pfizer Canada follows, ranking 12th, with \$160 million spent on R&D in 2004.
- ❖ The biotechnology industry is an important source of innovation for Canada’s pharmaceutical industry. In fact 80 percent of biotechnology R&D in Canada is directed to the development of health products. Canada spent an estimated \$2.5 billion on biotechnology research and development in 2004 and on average 68 percent of this spending has been undertaken by the industry. The federal government’s science and technology expenditures on biotechnology continued to climb from \$744 million in 2003/2004 to \$791 million in 2004/2005 representing 9 percent of total federal science and technology expenditures.
- ❖ Among the G-8 nations, Canada is rated as the most cost-competitive for new investment; as an example, clinical trials costs in Canada are on average 16% lower than in the USA.

This industry is composed of brand-name drug companies (which include biopharmaceutical companies) and generic drug companies. Both segments produce prescription and non-prescription drugs. The industry is clustered in the metropolitan areas of Montreal and Toronto where the location of R&D facilities is strongly influenced by the location of major biosciences clusters and by supportive government policies. Currently there are almost 500 products in the biopharmaceutical product pipeline from research through to market.<sup>3</sup>

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<sup>3</sup> Rx&D (<https://www.canadapharma.org/>)

<sup>4</sup> Statistics Canada (<http://www.statcan.gc.ca/start-debut-eng.html>)

<sup>5</sup> Ernst & Young (<http://www.ey.com/CA/en/Home>)

<sup>6</sup> Industry Canada (<http://www.ic.gc.ca>)

<sup>7</sup> <http://www.ic.gc.ca/eic/site/lsg-pdsv.nsf/eng/hn01656.html>

The Maternal Infant Child Youth Research Network (MICYRN)/Réseau de Recherche en Santé des Enfants et des Mères (RRSEM) was formed in 2006 to build capacity for high quality clinical research in Canada and beyond. MICYRN-RRSEM links 17 participating academic health centres, and hundreds of investigation teams across the country. MICYRN-RRSEM is committed to enhancing the productivity of the Canadian child-maternal research community, through sustaining and augmenting existing activities, and reducing impediments to multicentre research activity. A key contribution of MICYRN-RRSEM is information about child-maternal clinical research activity in Canada. This report provides information about Canada's involvement in clinical trials in children, with the intent to promote discussion about Canada's position in the global pediatric clinical trials movement, and to gauge interest in developing a national framework for multicentre clinical drug trials.

## Methods

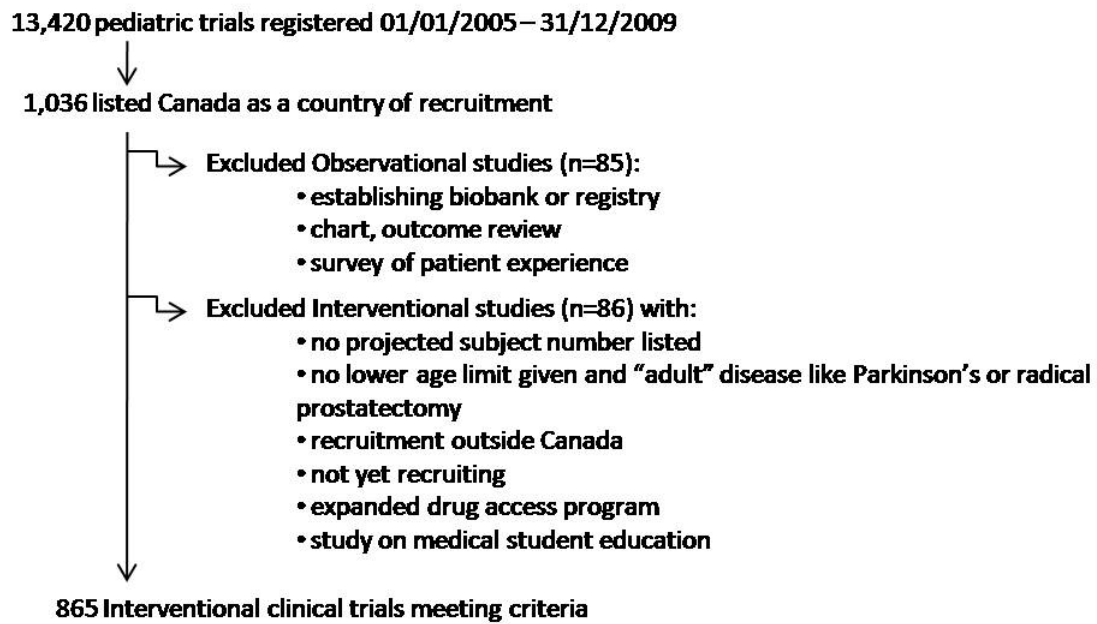
The World Health Organization (WHO) established an International Clinical Trials Registration Platform (ICTRP) following a Ministerial Summit on Health Research that took place in Mexico City, Mexico, in November 2004. Participants of the Summit called for the WHO to facilitate the establishment of: *“a network of international clinical trials registers to ensure a single point of access and the unambiguous identification of trials”*. As stated by the WHO, *“Registration of all interventional trials is considered to be a scientific, ethical and moral responsibility”*. This sentiment was supported by the International Committee of Medical Journal Editors (ICMJE) which had a parallel effort and in September 2005, implemented a policy that requires registration of clinically directive trials as a condition of consideration for publication in their journals. The WHO Registry Network is composed of 12 Registries which meet the reporting requirements of the ICMJE. Datasets from Registry data providers are updated regularly: weekly from the Australian New Zealand Clinical Trials Registry, ClinicalTrials.gov, and ISRCTN; and every four weeks from registries in China, India, Republic of Korea, Germany, Iran, Japan, Africa, Sri Lanka, and the Netherlands. Complete information about the Platform can be found at <http://www.who.int/ictrp/en/>.

The WHO Trial Registration Data Set currently includes 20 items. (see Appendix I for item list and definitions) The ICTRP Search Portal includes the ability to search on countries of recruitment; date of registration; recruitment status; and on phrases in the title, condition or intervention. In addition, the search portal identifies clinical trials in children by applying a set of filters specifically developed for this purpose. Briefly, about 80% of trials are identified by an initial screening with an "age" filter which identifies trials with searchable age information and flag records where participants include individuals between birth to 18 completed years. A second filter consisting of key terms is applied to records without searchable age information; it is stated that when trials are identified by keywords, the search may include trials that it should not or miss others. (for further information see <http://www.who.int/ictrp/child/search/en/index.html>)

This report covers a review of data retrieved from the WHO ICTRP to study pediatric interventional clinical trials over the past 5 years where Canada was listed as a 'country of recruitment'.

As at August 16<sup>th</sup>, 2010, the WHO database showed a total of 114,495 registered clinical trials, and of these, 18,511 (16 %) involved children. As indicated in Figure 1, this report reviews the registered interventional clinical trials where Canada was listed as a 'country of recruitment' during the period January 1<sup>st</sup>, 2005 through December 31<sup>st</sup>, 2009. About 10% of studies which were included had a lower age limit of ">14" or ">16 years" and involved clinical trials in conditions that could affect youth, such as trauma, cancer, or pregnancy and co-morbidities thereof.

**Figure 1 Selection algorithm for Canadian Pediatric Clinical Trials 2005-2009**



## Results

### Primary Sponsor

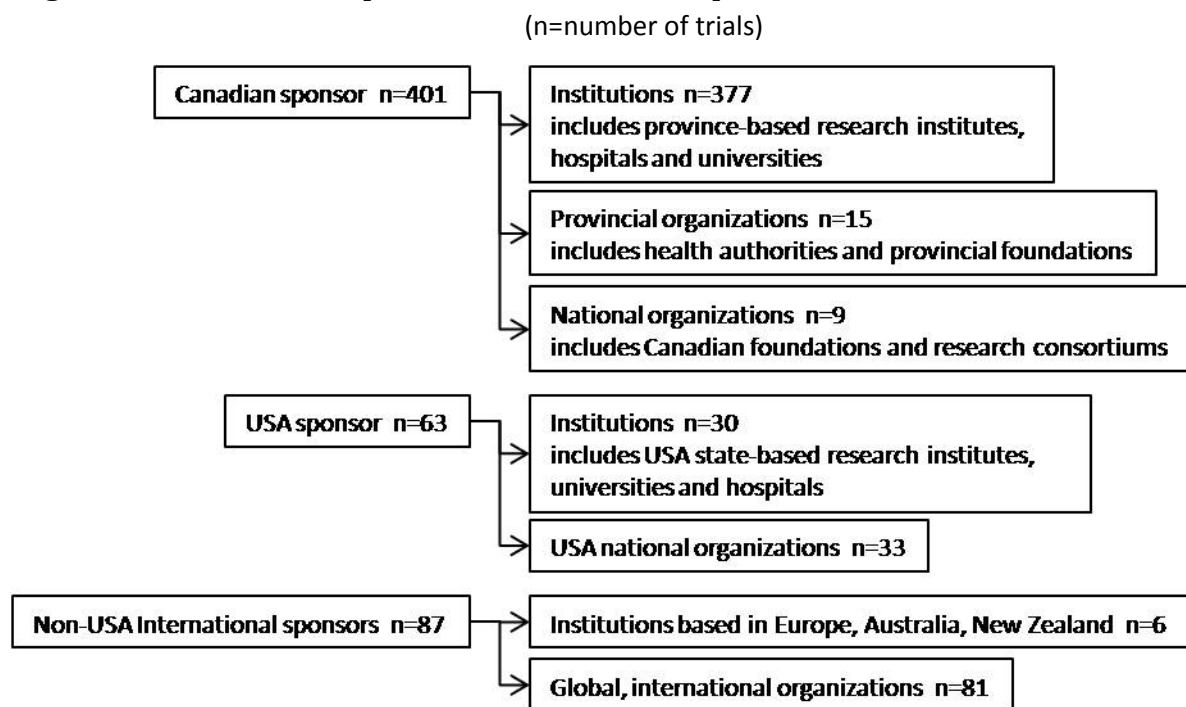
Overall, non-industry organizations were the primary sponsor for 551/865 (64%) of Canadian pediatric interventional clinical trials registered from 2005-2009. Industry was the primary sponsor for 314/865 (36 %) of the trials. (Table I) The larger number of trials registered in 2005 compared to subsequent years reflects the commencement of registration programs and the September 2005 ICMJE policy that required registration of clinically directive trials for investigators who wish to publish in ICMJE journals.

**Table I Primary Sponsor of Interventional Clinical Trials**

Year	Number	Academic	Industry
2005	221	154	67
2006	166	114	52
2007	154	94	60
2008	195	115	80
2009	129	74	55
	865	551	314

Figure 2 shows the distribution of trials by academic sponsors. Overall, Canadian sponsors were responsible for 401/551 (73%) of non-industry trials, with 377/401 (94%) of these being province-based academic institutions.

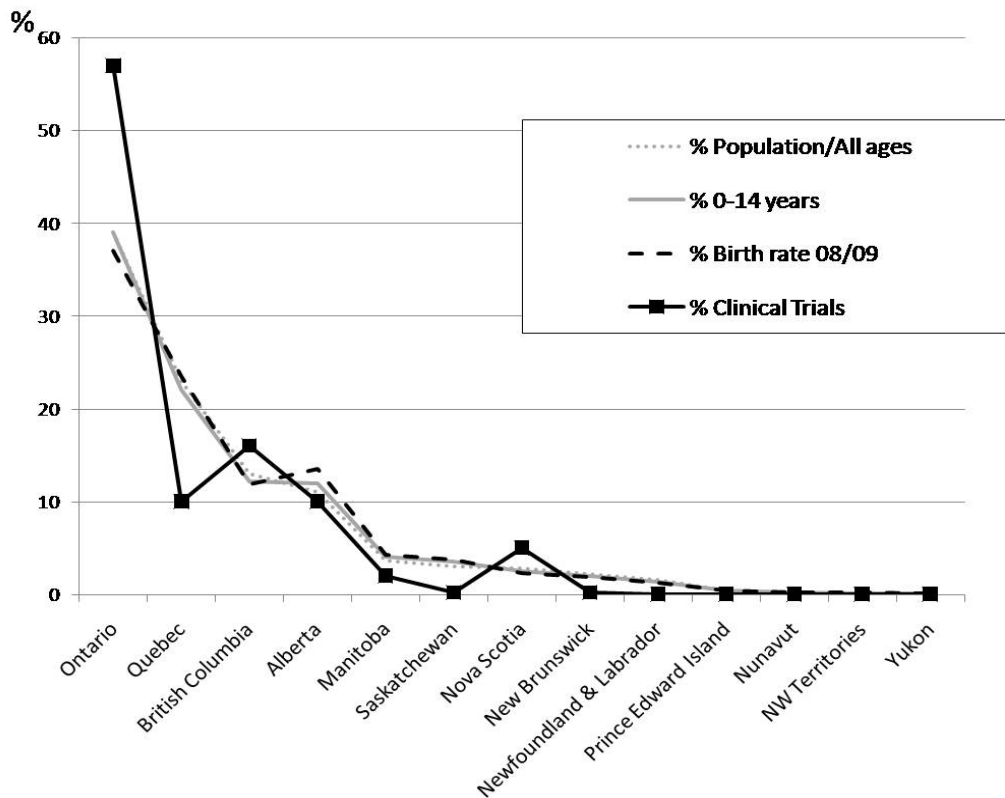
**Figure 2 Academic sponsors of interventional pediatric clinical trials in Canada**



Eighty of the 81 studies sponsored by global international groups were child cancer-related research consortiums, of which the Children’s Oncology Group (COG) accounted for 74.

Figure 3 shows the home province of the primary sponsor for academic trials. Generally the proportion of population, proportion of children aged 0-14 years, and birth rates correlate with the number of trials sponsored by academic institutions, with the exceptions of Ontario where there were more, and Quebec where there were fewer, numbers of studies than expected.

**Figure 3 Home Province of Primary Sponsor for Academic Trials**



Canadian academic health science centres with a focus on child and youth health which comprise the membership of the Canadian Council of Child Health Research (CCCHR) and the Maternal Infant Child Youth Research Network (MICYRN), were responsible for 287 (76%) of the 377 institution-sponsored trials. (Table II) With the exception of Ontario, health research involving children & youth was carried out by investigators at only a limited number of “non CCCHR-MICYRN” institutions. In BC these included 12 studies conducted by investigators at UBC and the Vancouver General Hospital who were not associated with the Child & Family Research Institute; and in Quebec, one study sponsored by the Jewish General Hospital. In Ontario other institutions included the Ottawa Hospital Research Institute

(13 studies), Toronto University Health Network (16 studies), Sunnybrook Hospital (9 studies), St. Michael's Hospital (7 studies), Mt. Sinai Hospital (6 studies), and University of Waterloo (5 studies).

**Table II Studies sponsored by member institutions of MICYRN and CCCHR**

Number of trials sponsored	Academic Institution			
	Child and Family Research Institute	University of British Columbia	Vancouver	British Columbia
49	Child and Family Research Institute	University of British Columbia	Vancouver	British Columbia
15	Women and Children's Health Research Institute	University of Alberta	Edmonton	Alberta
17	Institute of Maternal and Child Health	University of Calgary	Calgary	Alberta
1	Royal University Hospital	University of Saskatchewan	Saskatoon	Saskatchewan
7	Manitoba Institute of Child Health	University of Manitoba	Winnipeg	Manitoba
4	Children's Health Research Institute	University of Western Ontario	London	Ontario
25	McMaster Children's Hospital	McMaster University	Hamilton	Ontario
91	The Hospital for Sick Children	University of Toronto	Toronto	Ontario
7	Kingston General Hospital	Queen's University	Kingston	Ontario
19	Children's Hospital of Eastern Ontario (CHEO)	University of Ottawa	Ottawa	Ontario
0	Sudbury Regional Hospital	Laurentian University	Sudbury	Ontario
18	Montreal Children's Hospital Research Institute	McGill University	Montreal	Quebec
13	Le Centre de recherche du CHU Sainte-Justine	Université de Montréal	Montreal	Quebec
1	Sherbrooke University Hospital	Université de Sherbrooke	Sherbrooke	Quebec
2	Hospitalier Université Laval (CHUL)	Université de Laval	Quebec City	Quebec
18	IWK Health Centre	Dalhousie University	Halifax	Nova Scotia
0	Janeway Children's Health and Rehabilitation Centre	Memorial University	St. John's	Newfoundland

### Inter/national nature of pediatric trials

Canada is regularly involved as a site in multi-national pediatric clinical trials (Table III). Of the 865 studies conducted in Canada, 389 also involved USA sites; 210, European sites; and 154, Australian sites.

**Table III Canada's Involvement in International Interventional Clinical Trials**

Year	Total	Canada only	With USA sites	With European sites	With Australian sites
2005	221	128	83	50	30
2006	166	76	85	46	41
2007	154	67	73	40	26
2008	195	96	85	48	33
2009	129	62	63	26	24
	865	429	389	210	154

Table IV shows the international involvement of Academic- versus Industry-sponsored interventional clinical trials conducted in Canada.

**Table IV International Involvement of Academic- versus Industry-sponsored studies**

Year	Academic-sponsor			Industry-sponsor		
	Number	Conducted only in Canada	Included other countries	Number	Conducted only in Canada	Included other countries
2005	154	122	32	67	11	56
2006	114	71	43	52	5	47
2007	94	64	30	60	4	56
2008	115	83	32	80	11	69
2009	74	50	24	55	12	43
	551	390	161	314	43	271

The majority of studies where the primary sponsor was an academic organization were conducted solely in Canada. Canadian institutions and organizations sponsored only 20/161 (12%) of non-industry trials which included sites outside Canada. By contrast, the majority of industry-sponsored studies were multi-national. Only 44/314 (14%) industry-sponsored studies were conducted solely in Canada.

The 314 industry-sponsored clinical trials were conducted by 96 (ninety-six) different companies. Fifty-four percent of studies were conducted by 12 companies: GlaxoSmithKline (includes Stiefel) (n=41), Pfizer (includes Wyeth) (n=31), Novartis (n=21), UCB Inc (n=13), Astellas Pharma (n=10), Sanofi Aventis (n=10), Eli Lilly (n=9), Hoffman LaRoche (n=9), Galderma (n=7), Genzyme (n=7), Bayer (n=6), and Merck (includes Schering Plough) (n=6). A further 33 companies conducted 2-5 studies over the 5 year period (n=93 trials), and fifty-one companies conducted only 1 study (51/314) (16%). Trials Registration information did not include the number of sites within Canada (or any other country) at which studies were undertaken.

Table V shows information about the leading pharmaceutical companies in Canada, and the total number (interventional and observational) pediatric trials listing Canada as a country of recruitment.

**Table V Leading Pharmaceutical Companies in Canada<sup>8</sup>**

Rank	Leading Companies	R&D Location	Total Sales (\$Millions)	Market Share (%)	Number of Canadian paediatric trials (2005-2009)*
1	Pfizer	Montreal	2288	13.4	25
2	AstraZeneca	Montreal	1121	6.6	5
3	Johnson & Johnson	Toronto	1106	6.5	0
4	GlaxoSmithKline	Toronto	996	5.8	42
5	Apotex	Toronto	950	5.6	1
6	Wyeth	Montreal	675	4.0	8
7	Novartis	Toronto	647	3.8	22
8	Sanofi-Aventis	Quebec	625	3.7	10
9	Merck Frosst	Montreal	602	3.5	5
10	Bristol-Myers Squibb	Montreal	552	3.2	7

\*Figure for GSK includes Stiefel; Merck includes Schering Plough

The global nature of pediatric clinical trials is underlined by the observation that 78/314 (25%) of industry-sponsored trials listed an average of 12 countries (range 7-30) from which participants had or would be recruited at the time of registration, to enroll  $\leq 500$  study subjects. Table VI provides some examples of the multinational nature of Industry-sponsored pediatric trials.

**Table VI Multinational nature of Industry-sponsored trials**

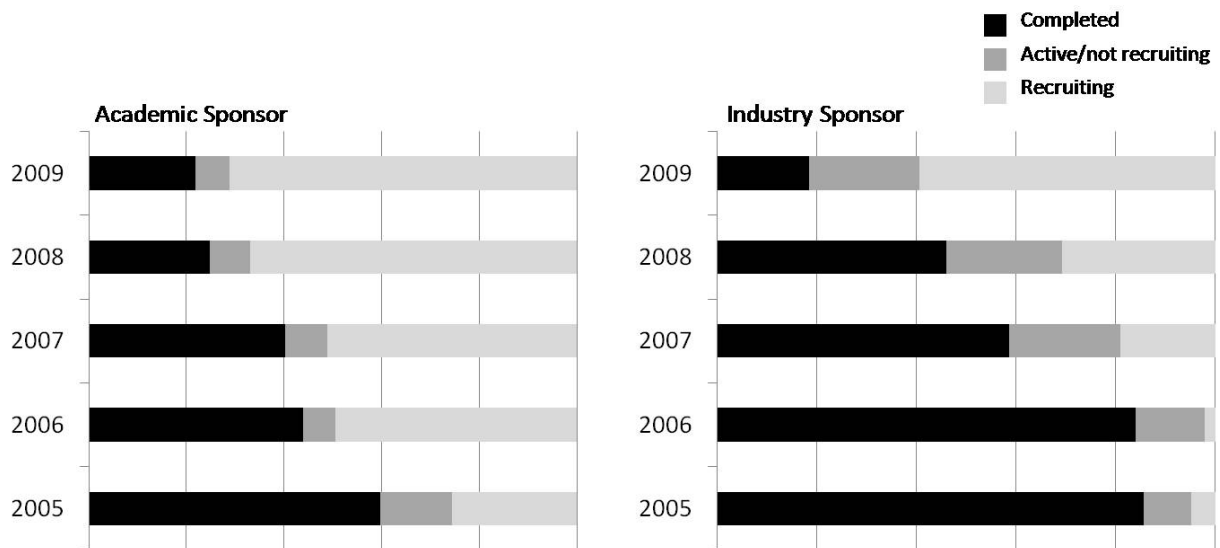
Disorder	Company	Enrollment Target	Number of Countries listed for recruitment
Hemophilia	Bayer	139	25
Arthritis	Novartis	122	21
Influenza treatment	Hoffman LaRoche	250	19
Kidney disease	Sanofi Aventis	25	11
Asthma	Glaxo Smith Kline	300	11
Epilepsy	UCB Inc	357	11

<sup>8</sup> Source: IMS Health: Canadian Drug Stores and Hospital Purchases Audit; and ICTRP

## Recruitment

Figure 4 illustrates the recruitment status of academic- compared to industry-sponsored trials. The impression that a higher proportion of industry- compared to academic-sponsored trials are completed in a timely fashion needs to be verified by prospective assessment. Note that the data for this report was linked to the date of trial registration, not commencement of enrolment. The Registry systems in place allow registration of studies at any time prior to initiation through to completion of enrolment, so it is possible to register a trial even when enrolment is completed. However, ICMJE journals have indicated that for trials beginning on or after July 1, 2005 they would only consider trials where registration occurred before the first patient was enrolled (“prospective registration”). If participant sponsors adhere to this policy, then the data presented in Figure 4 indicates industry-sponsored studies, the majority of which involve recruitment in multiple countries, are completed considerably more efficiently than studies sponsored by Canadian academic agencies, these principally being the CCCHR-MICYRN sites.

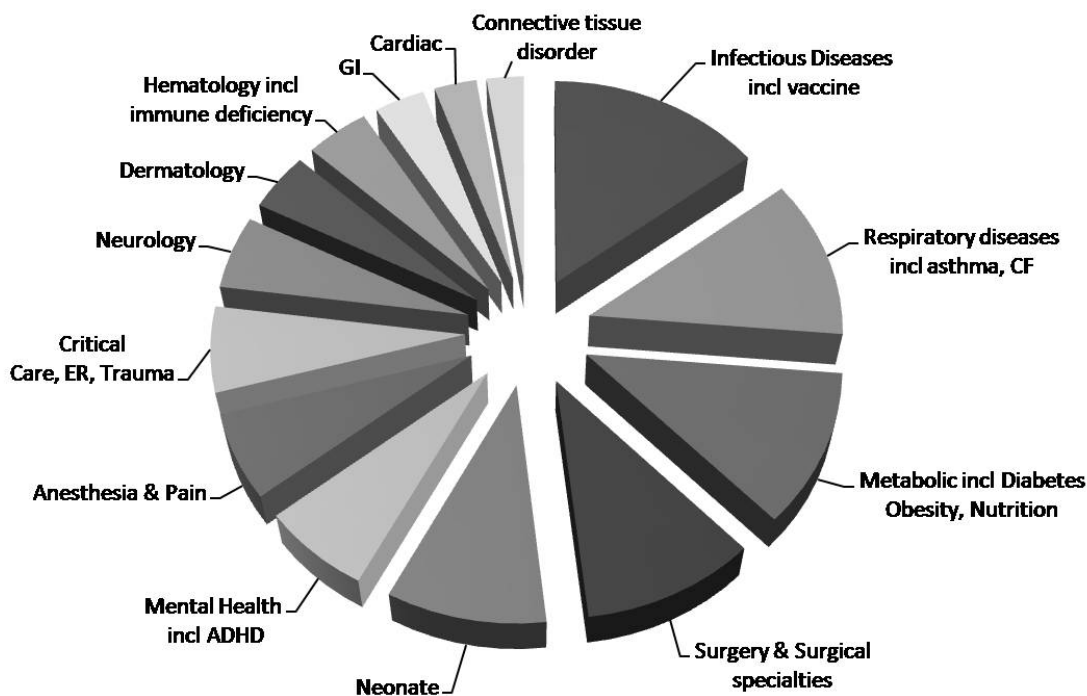
**Figure 4 Recruitment Status of Academic- compared to Industry-sponsored Trials**



## Subject of study

Fifteen health areas or conditions accounted for 90% of the interventional clinical trials (Figure 5). This information can be compared to the information on therapeutic products in development in Canada (Table VII).

**Figure 5 Health Conditions Studied by more than 15 clinical trials**



**Table VII Therapeutic products in development (Phase I to Phase III)<sup>9</sup>**

Cancer	63
Heart diseases	27
Neurological	20
Blood, skin and respiratory disorders	18
Infectious diseases	14
Growth and Digestive disorders	14
Eye conditions, Transplantation, Diabetes	9
AIDS/HIV and Autoimmune disorders	6
Bone and Muscle Diseases	5
<b>Total</b>	<b>176</b>

<sup>9</sup> Source: *The Biopharmaceutical Pipeline Report, Industry Canada, 2006*

## Comments

- The WHO ICTRP provides a rich resource of information about clinical trials
- There is a considerable amount of child-focused clinical trials activity in Canada and the vast majority of this is carried out by investigators at “CCCHR-MICYRN” institutions
- Industry-sponsored studies, the majority of which involve recruitment in multiple countries, appear to be completed considerably more efficiently than studies sponsored by Canadian academic agencies, these principally being the CCCHR-MICYRN sites.
- Canadian academic organizations are infrequent sponsors of multi-national pediatric interventional clinical trials.
- Pharmaceutical companies are in a position to compare Canada/Canadian sites/Canadian networks against other countries, in the ability to respond to and manage pediatric interventional clinical trials

## Appendix I World Health Organization Registration requirements <sup>10</sup>

The minimum amount of trial information that must appear in a register in order for a given trial to be considered fully registered, and the description of this information, is detailed following.

### 1. **Primary Registry and Trial Identifying Number**

Name of Primary Registry, and the unique ID number assigned by the Primary Registry to this trial.

### 2. **Date of Registration in Primary Registry**

Date when trial was officially registered in the Primary Registry. If relevant, also include the date of registration in the Partner Registry.

### 3. **Secondary Identifying Numbers**

Other identifiers besides the Trial Identifying Number allocated by the Primary Registry, if any. These should include:

- The Universal Trial Number (UTN)
- Identifiers assigned by the sponsor (record sponsor name and sponsor-issued trial number (e.g., protocol number))
- Other trial registration numbers
- Identifiers issued by funding bodies, collaborative research groups, regulatory authorities, ethics committees / institutional review boards, etc.

All secondary identifiers will have 2 elements: an identifier for the issuing authority (eg NCT, ISRCTN, ACTRN) plus a number.

There is no limit to the number of secondary identifiers that can be provided.

### 4. **Source(s) of Monetary or Material Support**

Major source(s) of monetary or material support for the trial (e.g., funding agency, foundation, company).

### 5. **Primary Sponsor**

The individual, organization, group or other legal entity which takes responsibility for initiating, managing and/or financing a study. The Primary Sponsor is responsible for ensuring that the trial is properly registered. The Primary Sponsor may or may not be the main funder.

### 6. **Secondary Sponsor(s)**

Additional individuals, organizations or other legal persons, if any, that have agreed with the primary sponsor to take on responsibilities of sponsorship. A secondary sponsor may have agreed:

- to take on all the responsibilities of sponsorship jointly with the primary sponsor; or
- to form a group with the primary sponsor in which the responsibilities of sponsorship are allocated among the members of the group; or

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<sup>10</sup> <http://www.who.int/ictrp/en/>

- to act as the sponsor’s legal representative in relation to some or all of the trial sites; or
- to take responsibility for the accuracy of trial registration information submitted.

**7. Contact for Public Queries**

Email address, telephone number, or postal address of the contact who will respond to general queries, including information about current recruitment status.

**8. Contact for Scientific Queries**

Email address, telephone number, or postal address, and affiliation of the person to contact for scientific queries about the trial (e.g., principal investigator, medical director employed by the sponsor). For a multi-center study, enter the contact information for the lead Principal Investigator or overall scientific director.

**9. Public Title**

Title intended for the lay public in easily understood language.

**10. Scientific Title**

Scientific title of the study as it appears in the protocol submitted for funding and ethical review. This title should contain information on population, intervention, comparator and outcome(s). Include trial acronym if available.

**11. Countries of Recruitment**

The countries from which participants will be, are intended to be, or have been recruited at the time of registration.

**12. Health Condition(s) or Problem(s) Studied**

Primary health condition(s) or problem(s) studied (e.g., depression, breast cancer, medication error).

If the study is conducted in healthy human volunteers belonging to the target population of the intervention (e.g. preventive or screening interventions), enter the particular health condition(s) or problem(s) being prevented.

**13. Intervention(s)**

For each arm of the trial record a brief intervention name plus an intervention description.

Intervention Name: For drugs use generic name; for other types of interventions provide a brief descriptive name.

- For investigational new drugs that do not yet have a generic name, a chemical name, company code or serial number may be used on a temporary basis. As soon as the generic name has been established, update the associated registered records accordingly.
- For non-drug intervention types, provide an intervention name with sufficient detail so that it can be distinguished from other similar interventions.

Intervention Description: Must be sufficiently detailed for it to be possible to distinguish between the arms of a study (e.g., comparison of different dosages of drug) and/or among similar interventions (e.g., comparison of multiple implantable cardiac defibrillators). For example, interventions involving drugs may include dosage form, dosage, frequency and

duration.

- If the intervention is one or more drugs then use the International Non-Proprietary Name for each drug if possible (not brand/trade names). For an unregistered drug, the generic name, chemical name, or company serial number is acceptable.
- If the intervention consists of several separate treatments, list them all in one line separated by commas (e.g., "low-fat diet, exercise").
- For controlled trials, the identity of the control arm should be clear. The control intervention(s) is/are the interventions against which the study intervention is evaluated (e.g., placebo, no treatment, active control). If an active control is used, be sure to enter in the name(s) of that intervention, or enter "placebo" or "no treatment" as applicable. For each intervention, describe other intervention details as applicable (dose, duration, mode of administration, etc).

#### 14. **Key Inclusion and Exclusion Criteria**

Inclusion and exclusion criteria for participant selection, including age and sex. Other selection criteria may relate to clinical diagnosis and co-morbid conditions; exclusion criteria are often used to ensure patient safety.

If the study is conducted in healthy human volunteers not belonging to the target population (e.g., a preliminary safety study), enter "healthy human volunteer".

#### 15. **Study Type**

Study type consists of:

- Type of study (interventional or observational)
- Study design including:
  - Method of allocation (randomized/non-randomized)
  - Masking (is masking used and, if so, who is masked)
  - Assignment (single arm, parallel, crossover or factorial)
  - Purpose
- Phase (if applicable)

#### 16. **Date of First Enrollment**

Anticipated or actual date of enrollment of the first participant.

#### 17. **Target Sample Size**

Number of participants that this trial plans to enrol in total.

#### 18. **Recruitment Status**

Recruitment status of this trial:

- Pending: participants are not yet being recruited or enrolled at any site
- Recruiting: participants are currently being recruited and enrolled

- Suspended: there is a temporary halt in recruitment and enrollment
- Complete: participants are no longer being recruited or enrolled
- Other

#### 19. **Primary Outcome(s)**

Outcomes are events, variables, or experiences that are measured because it is believed that they may be influenced by the intervention.

The Primary Outcome should be the outcome used in sample size calculations, or the main outcome(s) used to determine the effects of the intervention(s). Most trials should have only one primary outcome.

For each primary outcome provide:

- The name of the outcome (do not use abbreviations)
- The metric or method of measurement used (be as specific as possible)
- The time point(s) of primary interest

Example: Outcome Name: Depression; Metric/method of measurement: Beck Depression Score; Timepoint: 18 weeks following end of treatment

#### 20. **Key Secondary Outcomes**

Secondary outcomes are outcomes which are of secondary interest or that are measured at timepoints of secondary interest. A secondary outcome may involve the same event, variable, or experience as the primary outcome, but measured at timepoints other than those of primary interest.

As for primary outcomes, for each secondary outcome provide:

- The name of the outcome (do not use abbreviations)
- The metric or method of measurement used (be as specific as possible)
- The time point(s) of interest